PATENT SPECIFICATION (11) 1237008

1237008

NO DRAWINGS

(21) Application No. 60083/68 (22) Filed 18 Dec. 1968

(23) Complete Specification filed 17 Dec. 1969

(45) Complete Specification published 30 June 1971

(51) International Classification C 07 d 27/38 57/00

(52) Index at acceptance

ERRATA

SPECIFICATION No. 1,237,008

Page 1, line 67, *for* "morpholine" *read* "morpholino"

Page 2, line 26, *for* "of" *read* "or"

Page 2, line 35, *for* "prapared" *read* "prepared"

Page 2, line 54, *for* "eiether" *read* "either"

Page 2, line 72, *after* "corresponding" *insert* "unsaturated"

Page 2, line 93, *for* "pyridines." *read* "pyridones."

Page 2, renumber line 100 to read 95

Page 3, line 25, *for* "saturated" *read* "unsaturated"

Page 4, line 29, *for* "the neither" *read* "then either"

Page 5, lines 28 and 29, *for* "etheral" *read* "ethereal"

Page 5, line 33, *for* "-(3-3" *read* "3-(3-"

Page 5, line 39, *for* "$C_{21}H_{24}NO_{.5}$." *read* "$C_{21}H_{24}NO_5$."

Page 5, line 40, *for* "N, 7.08" *read* "N, 7.29"

Page 5, line 58, *for* "boron" *read* "brown"

Page 5, line 59, *for* "(M.p. 13—155°," *read* "(M.p. 153—155°,"

Page 5, line 62, *for* "20°)." *read* "20%)."

Page 6, line 2, *after* "done" *insert* "("

Page 6, lines 5, 27 and 29, *for* "etheral" *read* "ethereal"

Page 6, line 23, *for* "solutions" *read* "solution"

Page 6, line 52, *for* "etheral" *read* "ethereal"

Page 6, line 57, *for* "239—241." *read* "239—241°."

Page 7, line 5, *for* "3.29" *read* "3.29 g."

Page 7, line 22, *for* "etheral" *read* "ethereal"

Page 7, line 73, *for* "and" *read* "to"

Page 7, line 77, *after* "-1-" *insert* "phenyl-"

Page 8, line 31, *for* "bromobenzen" *read* "bromobenzene"

Page 8, line 60, *for* "isoproanol-" *read* "isopropanol"

Page 8, line 85, *for* "CHR^4.," *read* "CHR^4,"

Page 8, line 111, *for* "-indoline" *read* "-indolinone"

Page 9, line 44, *after* "group," *insert* "with"

THE PATENT OFFICE
8th November 1971

SEE ERRATA SLIP ATTACHED

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C2C 174—198—272 213 220 226 22Y 246 250 251 25Y 29X 29Y 304 30Y 322 323 32Y 351 352 3A10E3D1 3A10E5E 3A13A3A4 3A13A3B1 3A13A3H2 3A14A3A 3A14A5 3A14A8D 456 45Y 620 650 761 762 790 79Y LK NL

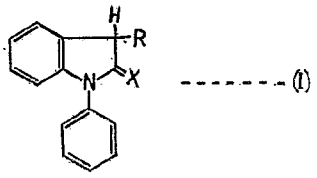
(72) Inventors ANTONIO CANAS-RODRIGUEZ and PETER RODWAY LEEMING

(54) NOVEL INDOLINE DERIVATIVES

(71) We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to N - phenyl - indoline derivatives, and is particularly concerned with 3 - aminoalkyl - 1 - phenyl indolines and 2 - indolinones which we have found to be useful for their action on the central nervous system and on the cardiovascular system. In particular we have discovered that many of these compounds have useful anti-depressant and/or antihypertensive activity, particularly when administered orally.

The compounds of the invention are those having a structural formula represented by:



(I)

where: (i) R represents *either* a group: $-C_nH_{2n}-NR^1R^2$, in which R^1 and R^2 each represent a hydrogen atom, a lower alkyl group or a benzyl group, or together with the nitrogen atom to which they are attached form a saturated heterocyclic ring containing at least 4 carbon atoms in the ring which, if it contains a further nitrogen atom in the ring, may be substituted at such nitrogen atom with a lower alkyl or hydroxyalkyl group or a benzyl group, and C_nH_{2n} represents a lower alkylene group separating the nitrogen atom from the indoline ring by at least 2 carbon atoms;

or a group: $-C_mH_{2m}-\overset{\frown}{CHR^4}$, in which m is from 0 to 4 and R^4 represents a bivalent group containing up to (7—m) carbon atoms and forming with the carbon atom to which it is attached a saturated heterocyclic ring containing at least 4 carbon atoms and at least one nitrogen atom, any such nitrogen atom being separated from the indoline ring by at least 2 carbon atoms and optionally carrying a lower alkyl or hydroxyalkyl group or a benzyl group;

(ii) X represents either an oxygen atom or two hydrogen atoms; and

(iii) any benzene ring (including the fused benzene ring) in the structural formula or in R^1, R^2 or R^4 may be substituted with one or more halogen atoms, lower alkyl or alkoxy groups, trifluoromethyl groups, nitro groups, hydroxyl groups or sulphamoyl or N - substituted sulphamoyl groups;

and the pharmaceutically acceptable acid addition salts of such compounds.

In this specification, the term "lower", when applied to alkyl, alkoxy, hydroxyalkyl or alkylene groups, indicates that such groups contain not more than 8 carbon atoms, in a straight or branched chain.

When R^1 and R^2 form a saturated heterocyclic ring with the nitrogen atom to which they are attached, such ring may constitute, for example, a pyrrolidino, piperidino, piperazino, morpholine or hexamethylenimino group.

In the group C_nH_{2n}, n must of course be at least 2 and is preferably not more than 4. It may be, for example, an ethylene, propylene, trimethylene or tetramethylene group. Preferably it is an ethylene or trimethylene group.

Where R is a group $-C_mH_{2m}-\overset{\frown}{CHR^4}$, then such group may be, for example, a 3 - pyrrolidyl group, a 2- or 3 - pyrrolidyl - C_{1-4} alkyl group, a 3- or 4 - piperidyl group,

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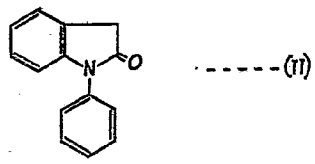
a 2-, 3- or 4 - piperidyl—C_{1-3} alkyl group (or analogous imidazolidinyl, piperazinyl, morpholinyl and saturated azepinyl and diazepinyl groups containing a maximum of 8 carbon atoms in which any ring nitrogen atom is separated from the indoline ring by at least 2 carbon atoms), or N - lower alkyl, N - lower hydroxyalkyl or N - benzyl derivatives thereof. In particular, R may be a 3- or 4 - piperidyl group, or a 2-, 3- or 4 - piperidyl - methyl group, or a 1 - lower alkyl or 1 - benzyl derivative of such a group.

Many compounds of the invention have marked activity on the adrenergic nervous system of experimental animals, and have properties in common with anti-depressant drugs. In particular the latter antagonise the sedation induced in rats by intraperitoneally injected tetrabenazine, potentiate the response to low frequency electrical stimulation of the nictitating membrane of the cat, potentiate the effects of injected adrenaline or noradrenaline on the blood pressure of the cat, and reverse the hypothermia caused by intraventricularly injected noradrenaline of by subcutaneously injected reserpine, in the mouse.

Also, many compounds of the invention have a marked effect on the cardiovascular system of experimental animals, in particular an anti-hypertensive effect when tested in conscious hypertensive rats or dogs.

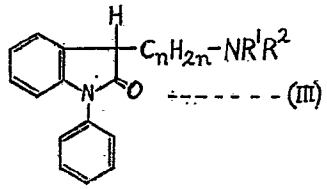
The compounds of the invention may be prapared by a number of methods including the following:

(1) A 3 - unsubstituted 1 - phenyl - 2 - indolinone of the formula:



.....(II)

(in which any benzene ring may be substituted, as already described) may be reacted with an alkali metal (or a hydride, amide or alkoxide thereof) in a suitable solvent e.g. toluene or dimethyl formamide, to form an alkali metal derivative of the indolinone, and then with a halogenated amine of the formula Hal—C_nH_{2n}—NR^1R^2, where neither R^1 nor R^2 is hydrogen, to yield a compound of the formula:



.....(III)

However, in this reaction substantial amounts of 3,3 - bis (aminoalkyl) derivatives are formed and it is preferred to use, instead of an alkali metal, eiether thallium metal or a thallous alkoxide, since under these conditions much higher proportions of 3 - mono (aminoalkyl) derivatives are formed. (2) A compound of the formula II above may be reacted with an aldehyde or ketone having the formula:

$R^3 . CO . C_{n-1}H_{2n-2}—NR^1R^2$ (IVA)

or

$R^3 . CO . C_{m-1}H_{2m-2}—R^5$ (IVB)

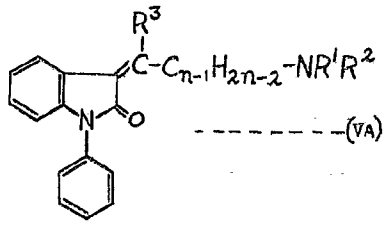
or

$0=\overbrace{C\ R^6}$ (IVC)

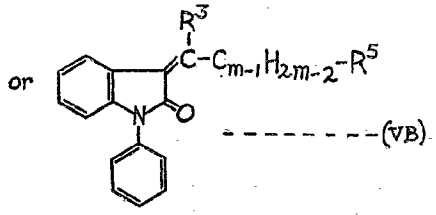
where $C_{n-1}H_{2n-2}$ and $C_{m-1}H_{2m-2}$ represent, respectively, the groups C_nH_{2n} and C_mH_{2m} (as already defined, m being at least 1) from which a terminal group —CHR^3 — has been abstracted, R^1 and R^2 are as already defined or, when they form a heterocyclic ring, may form a corresponding ring; R^3 represents a hydrogen atom or an alkyl group containing not more than 8_{-n} or 4_{-m} carbon atoms respectively, R^5 represents the group $\overbrace{—CHR^4}$ as already defined or an unsaturated derivative thereof; and R^6 represents the group R^4 as already defined or an unsaturated derivative thereof; provided that, in the said aldehyde or ketone, neither R^1 nor R^2 is hydrogen, and any secondary nitrogen atom in R^5 or R^6, or in R^1 and R^2 together, is substituted with a lower alkyl or hydroxyalkyl group or a benzyl group.

Ketones of the formula IVC are saturated or unsaturated heterocyclic ketones and include, for example, N - substituted 3 - pyrrolidones, 3- or 4- piperidones (and analogous imidazolinones, piperazinones, azepinones and diazepinones) as well as unsaturated compounds such as 3- or 4 - oxo - 1, 2 - dihydro - pyridine, and N - substituted 4 - pyridines.

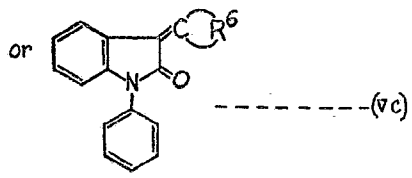
In the method (2) the product of the reaction is a compound of the formulae:



(VA)



(VB)

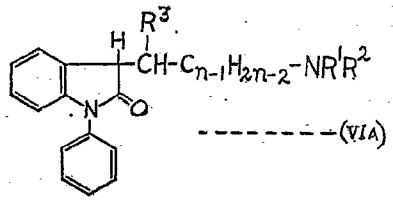


(VC)

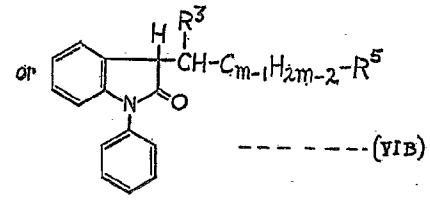
corresponding to the use of a compound of the formula IVA, IVB or IVC, respectively, as starting material, the compound of formula VC being, for example, a 1 - phenyl - 3 - (N - substituted) piperidylidene - 2 - indolinone.

The compound of the formula VA, VB or VC is then reduced catalytically with hydrogen, or reduced with sodium borohydride, any unsaturated heterocyclic ring present being reduced by catalytic hydrogenation, either simultaneously or (in better yield) subsequent to sodium borohydride reduction.

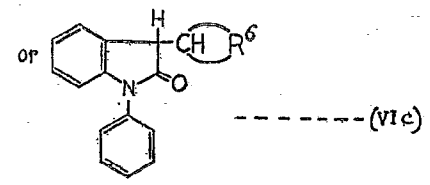
The compounds of the formula VA, VB and VC are novel compounds, as are partially reduced compounds, i.e. compounds of the formulae:



(VIA)



(VIB)



(VIC)

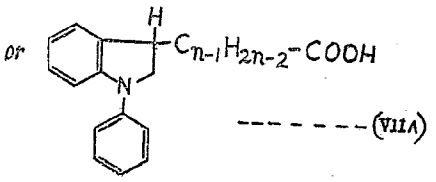
where R^1 and R^2 form an unsaturated ring, and R^5 and R^6 are saturated derivatives of the groups $-\overbrace{CHR^4}$ and R^4, respectively

(3) Compounds of the formula I in which R is $-C_nH_{2n}NR^1R^2$ and R^1 is benzyl may be converted to compounds in which R^1 is hydrogen by reduction with hydrogen in the presence of a palladium catalyst, thereby removing the benzyl group.

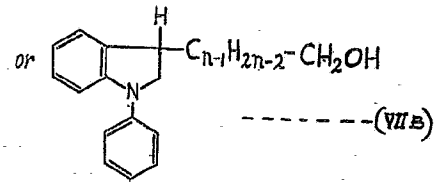
Similarly compounds of formula I in which the group R contains an N - benzyl - substituted saturated heterocyclic ring may be converted to the corresponding N - unsubstituted compounds.

(4) Compounds of the formula I in whch X is an oxygen atom may be converted to compounds in which X is H_2 by reduction with diborane.

(5) Compounds of formula I in which R is $-C_nH_{2n}NR^1R^2$ and X is two H atoms may also be prepared from 1 - phenyl - 2 - indolinyl carboxylic acids or alcohols of the formulae:



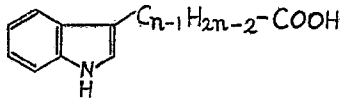
(VIIA)



(VIIB)

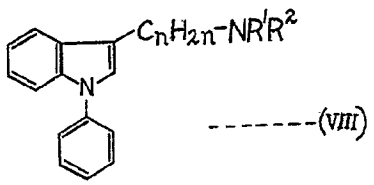
where $C_{n-1}H_{2n-2}$ now represents the group C_nH_{2n} from which a terminal $—CH_2—$ group has been abstracted, either by converting the acid (or a suitable ester thereof) to the appropriate amide by reaction with ammonia or an amine of the formula R^1R^2NH and reducing the amide with lithium aluminium hydride, or by converting the alcohol to the required amine by reaction of a suitable derivative thereof (in which the —OH group is replaced by a 'leaving' group, such as a halogen atom or *p* - toluene - sulphonyloxy group) with ammonia or an amine of the formula R^1R^2NH.

Compounds of formula VIIA and B are prepared from 3 - indolyl carboxylic acids of the formula:



(or suitable esters thereof) by hydrogenation at a sufficiently high pressure (e.g. 4000 p.s.i.) in the presence of Raney nickel, as described by Kornfeld *et al* in J. Amer. Chem. Soc. vol. 78, page 3096 (1956), or at lower pressure in the presence of a nickel, palladium or platinum catalyst freshly prepared *in situ*, to yield the corresponding 3 - indolinyl carboxylic acid or ester which is the neither phenylated directly by the Ullmann reaction, with a phenyl halide and copper powder, or first reduced with lithium aluminium hydride to the alcohol and then phenylated.

(6) Compounds of the formula I in which X is two H atoms and R is $—C_nH_{2n}—NR^1R^2$ may also be prepared from the corresponding indolyl compounds of the formula:—



by reduction with sodium in liquid ammonia. The compounds of formula VIII are readily prepared by the following methods (analogous to those described in co-pending application no. 34722/68 (Serial No. 1,220,628) and in United States Patent Specification No. 2,642,438): (A) from N - phenyl - indole - 3 - carboxaldehydes by reaction with aliphatic aldehydes, ketones or esters having an alpha-methylene group, or with an alpha - halo - ester (Reformatsky reaction), to give the corresponding 3 - (3 - indolyl) acrylic aldehydes or esters, which are catalytically hydrogenated, reacted with an appropriate amine to form the corresponding 3 - (3 - indolyl) propionamides or propylidene - imines and reduced to the corresponding amines in which the nitrogen atom is separated from the indoline ring by 3 carbon atoms;

(B) from N - phenyl - indole - 3 - carboxaldehydes by Grignard reaction with haloamines of the formula hal $—C_{n-1}H_{2n-2}—NR^1R^2$, and catalytic hydrogenation of the unsaturated amine so formed;

(C) by the Fisher indole synthesis from N,N - diphenyl hydrazones of amino- or hydroxy- aldehydes of the formula $O=CH—CH_2—C_nH_{2n}—X^1$, where X^1 is either $—NR^1R^2$ (in which case compounds of formula VIII are formed directly), or a hydroxyl group, which is subsequently converted to halogen, or to any other suitable "leaving" group such as *p*-toluene-sulphonyloxy, and then reacted with an amine of the formula HNR^1R^2;

(D) from N - substituted indole - 3 - carboxaldehydes, or monophenyl hydrazones, by the methods described in (A), (B) or (C), followed by phenylation by the Ullmann reaction.

The compounds of the invention exist in D and L optically active isomeric forms, by virtue of the asymmetric carbon atom at position 3 in the indoline nucleus, and the invention comprehends the compounds in the separated D and L forms, as well as the racemic DL-mixtures produced by the above methods.

Acids from which pharmaceutically acceptable addition salts of the compounds of the invention can be prepared are those which form non-toxic addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide hydroiodide, sulphate or bisulphate, phosphate or acid phosphate acetate, maleate, fumerate, lactate, tartrate, citrate, gluconate, saccharate and p-toluene sulphonate salts.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example intramuscularly or subcutaneously. For parenteral adminstration, they are best used in the form of a sterile

aqueous solution which may contain other solutes, for example enough salts or glucose to make the solution isotonic.

The invention is illustrated by the following Examples of the preparation and characterisation of compounds of the invention. In these Examples, all temperatures are given in °C.

EXAMPLE I

To 1 - phenyl - 2 - indolinone (20.9 g., 0.1 mol.) dissolved in hot, dry benzene (200 mls.) thallous exthoxide (24.5 g. 0.1 mol.) was added. On cooling a heavy precipitate of the thallous derivative was obtained. Dry dimethylformamide (150 ml.) was added to the mixture followed by 3 - dimethylamino - propyl chloride (13.36 g., 0.11 mol.), freshly prepared form the corresponding hydrochloride and KOH pellets. The mixture was heated to 90° and stirred for 6 hours, after which the solvents were evaporated in vacuo. Traces of dimethylformamide and alkylating reagent were eliminated by azeotropic distillation *in vacuo* with xylene. The residual oil was treated with water and extracted with ether, and the etheral liquors were filtered through a small layer of active alumina. The etheral solution was dried and treated with an etheral solution of anhydrous oxalic acid. A white precipitate was obtained which was thoroughly washed with ether and recrystallised from isopropanol five times to give 2g. of pure - *(3 -3 dimethylaminopropyl) - 1 - phenyl - 2 - indolinone hydrogen oxalate* as a white solid containing water of crystallisation (half a molecule.) M.pt: 154—155°

Analysis:
Calcd. for: $C_{21}H_{24}NO_{5}.1/2H_2O$:
C, 64.10; H, 6.40; N, 7.08
Found: C, 64.33; H, 6.37; N, 7.08

The product of this Example has been found to have properties in common with antidepressant drugs in experimental animals.

EXAMPLE II

N - Methyl - piperidine (9.9 g., 0.1 mol.) was added to a mixture of 1 - phenyl - 2 - indolinone (20.9 g., 0.1 mol.) and 4 - pyridine - aldehyde (10.6 g., 0.1 mol.) in dry benzene (360 mls.). The reactants were heated under reflux for thirty minutes with simultaneous azeotropic separation of the water formed during the reaction (Dean and Stark apparatus). The theoretical amount of water was collected and the mixture was evaporated to dryness. The residue was triturated with methanol. A boron solid (M.p. 13—155°, 19.7 g., 66%) separated, and upon repetition of this procedure a second crop of material was obtained (M.p. 150—151°; 6 g., 20°). Recrystallisation of the combined crops from ethanol gave *1 - phenyl - 3 - (4 - pyridylmethylidene) - 2 - indolinone* as a yellow solid M.pt: 157—157.5°.

Analysis:
Calcd for: $C_{20}H_{14}N_2O$:
C, 80.51; H, 4.73; N, 9.39%
Found: C, 80.82; H, 4.89; N, 9.26%

EXAMPLE III

The conditions used and quantities of reagents were similar to those described in Example II, but 3 - pyridine - aldehyde was substituted for 4 - pyridine - aldehyde and triethylamine was employed as the basic catalyst. The yield of *1 - phenyl - 3 - (3 - pyridylmethylidene) - 2 - indolinone* was 10 g. Recrystallisation from ethanol gave a yellow solid. M.p.: 87—89°.

Analysis
Calcd. for: $C_{20}H_{14}N_2O$:
C, 80.51; H, 4.73; N, 9.39%
Found: C, 80.58; H, 4.81; N, 9.40%

EXAMPLE IV

Conditions similar to those of Example II were used, and the same quantities of reagents, except that 2 - pyridine - aldehyde was used instead of 4 - pyridine - aldehyde, and pyrrolidine (7 ml.) as the basic catalyst. The crude yield of *1 - phenyl - 3 - (2 - pyridylmethylidene) - 2 - indolinone* was 24.5 g. Recrystallisation from ethanol gave a deep yellow solid M.p. 146.5—147.5°.

Analysis:
Calcd. for: $C_{20}H_{14}N_2O$:
C, 80.51; H, 4.73; N, 9.39%
Found: C, 79.94; H, 4.63; N, 9.74%

EXAMPLE V

A mixture of 1 - phenyl - 2 - indolinone (0.1 mol. 20.9 g.), 1 - benzyl - 4 - piperidone (0.1 mol. 18.1 g.) and piperidine (0.1 mol. 8.13 g.=9.45 mls.) in 100 mls. of methanol was heated under reflux for two hours. The reaction mixture was evaporated *in vacuo* and the residue was treated with 60—80° petrol (200 mls.) and evaporated *in vacuo* to remove traces of piperidine. The residual oil was triturated with dry ether and the solid which formed was filtered and recrystallised from 100—120° petrol. (Yield: 18.1 g.). Two further crystallisations from the same solvent gave pure *3 - (1 - benzyl - 4 - piperidylidene) - 1 - phenyl - 2 - indolinone* as yellow crystals. M.p.: 125—127°.

Analysis:
Calcd. for: $C_{26}H_{24}N_2O$:
C, 82.07; H, 6.36; N, 7.36%
Found: C, 82.20; H, 6.62; N, 7.35%

EXAMPLE VI

Similar conditions to those of Example V were used, and the same quantities of re-

agents, except that 1 - methyl - 4 - piperidone 11.3 g., 0.1 mol.) was used instead of the 1 - benzyl derivative. The crude hydrochloride (30 g.) was prepared by treating the etheral solution of the base with etheral HCl. Three recrystallisations from absolute ethanol gave pure *3 - (1 - methyl - 4 - piperidylidene) - 1 - phenyl - 2 - indolinone hydrochloride* as a pale yellow solid. M.p.: 222—225°.

Analysis:

Calcd. for: $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20%
Found: C, 78.80; H, 6.60; N, 9.02%

Example VII

1 - Phenyl - 3 - (4 - pyridylmethylidene) - 2 - indolinone (6.1 g., prepared as in Example II) was dissolved in aqueous ethanol (3:1, 100 mls.) and this solution was acidified with conc. HCl to pH 2. The mixture was hydrogenated over PtO_2 (1 g.) at 50 p.s.i. and 50° until the uptake of hydrogen ceased. The clear solutions resulting after filtration of the catalyst was evaporated to dryness to give an oil which was extracted into ether after basification with 5N NaOH. The etheral extracts were dried over Na_2SO_4 and treated with etheral maleic acid solution, whereupon an oil precipitated. This was triturated with isopropanol until crystallisation occurred.

The white solid was recrystallised from ethanol to yield 1.5 g. of *1 - phenyl - 3 - (4 - piperidylmethyl) - 2 - indolinone hydrogen maleate*. M.p. 186—188°.

Analysis:

Calcd. for: $C_{24}H_{26}NO_5$: C, 68.23; H, 6.20; N, 6.63%
Found: C, 68.20; H, 6.14; N, 6.50%

Example VIII

(A) 1 - Phenyl - 3 - (4 - pyridylmethylidene) - 2 - indolinone (0.035 mol, prepared as in Example II was suspended in dry ethanol and $NaBH_4$ (0.035 mol.) was added with cooling and stirring. After fifteen minutes a clear yellow solution was obtained. The excess of $NaBH_4$ was decomposed with the minimum amount of dilute acetic acid solution and the mixture was then evaporated to a small volume, acidified with excess dilute acetic acid and extracted with ether. From the etheral extracts *1 - phenyl - 3 - (4 - pyridylmethyl) - 2 - indolinone hydrochloride* was obtained by the addition of ethereal HCl. The white solid which separated was recrystallised from ethanol/40—60° petrol. Yield: 62%. M.p.: 239—241. A further recrystallisation from the same solvent gave white crystals. M.p.,: 249—251°.

Analysis:

Calcd. for: $C_{20}H_{17}ClN_2O$: C, 71.32; H, 5.09; N, 8.32%
Found: C, 71.00; H, 4.99; N, 8.34%

(B) 1 - Phenyl - 3 - (4 - pyridylmethyl) - 2 - indolinone hydrochloride from (A) (0.01 mol.) was suspended in ethanol (60 mls.) and HCl (0.01 mol.) and sufficient water to achieve solution was added (15 ml.). The mixture was hydrogenated for four hours at 50 p.s.i. at room temperature over platinum oxide (300 mgs.). After filtration of the catalyst the solution was basified with $NaHCO_3$ solution and extracted with chloroform. The extracts were washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to dryness. The oil was taken up in the minimum quantity of methanol and ethereal maleic acid solution was added. This gave a precipitate of white crystals. M.p.: 174—178°. Yield: 90%. One recrystallisation from ethanol-ether yielded 54% of *1-phenyl - 3 - (4 - piperidylmethyl) - 2 - indolinone hydrogen maleate* M.p.: 186—188°.

Analysis:

Calcd. for: $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63%
Found: C, 68.10; H, 6.14; N, 6.37%

Examples IX and X

In similar conditions to those described in Example VII the following compounds were obtained:

(IX) *1 - Phenyl - 3 - (3 - piperidylmethyl) - 2 - indolinone hydrogen maleate*

This was prepared from 1 - phenyl - 3 - (3 - pyridylmethylidene) - 2 - indolinone (9.5 g, prepared as in Example III) as a white crystalline solid and recrystallised from ethanol (4.0 g.). M.p.: 155—158°.

Analysis:

Calcd. for: $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63%
Found: C, 68.18; H, 6.33; N, 6.99%

(X) *1 - Phenyl - 3 - (2 - piperidylmethyl) - 2 - indolinone hydrochloride*

This was prepared from 1 - phenyl - 3 - (2 - pyridylmethylidene) - 2 - indolinone (14 g, prepared as in Example IV) as a white crystalline solid (12.6 g.) and recrystallised from isopropanol. M.p.: 233.5—238.5°.

Analysis:

Calcd. for: $C_{20}H_{23}ClN_2O$: C, 70.10; H, 6.78; N, 8.17%
Found: C, 70.06; H, 6.90; N, 7.88%

Example XI

3 - (1 - Methyl - 4 - piperidylidene) - 1-phenyl - 2 - indolinone (17 g, prepared as in Example VI) was hydrogenated in ethyl acetate (200 mls.) with 10% palladium on charcoal (0.7 g.) at 50 p.s.i. and 50°. The filtered solution gave a white solid on evaporation which was crystallised from 60—

80° petrol to give 12.5 g. of white crystals. M.p.; 116—117°.

A further crystallisation of 5 g. of the product raised the melting point to 118—120°, giving 3.29 of pure *3 - (1 - methyl - 4 - piperidyl) - 1 - phenyl - 2 - indolinone.*

Analysis:

Calcd. for: $C_{20}H_{22}N_2O$:
C, 78.4; H, 7.24; N, 9.14
Found: C, 78.23; H, 7.03; N, 8.9

Example XII

3 - (1 - Benzyl - 4 - piperidylidene) - 1 - phenyl - 2 - indolinone

(10 g, prepared as in Example V) in acetic acid (100 ml.) was hydrogenated over 10% palladium on charcoal (0.20 g.) at 60 p.s.i. and 60°, until the uptake of hydrogen ceased. The filtered solution was evaporated to dryness *in vacuo* and the residue was basified with 5N NaOH and extracted into ether. The dried ethereal liquors were treated with ethereal HCl to yield about 9.5 g. of a white solid which proved to be a mixture of 3 - (1 - benzyl - 4 - piperidyl)-1 - phenyl - 2 - indolinone hydrochloride and *1 - phenyl - 3 - (4 - piperidyl) - 2 - indolinone hydrochloride*, in which the latter predominated. After recrystallisation three times from ethanol, a yield of 1.5 g. of pure *3 - (1 - benzyl - 4 - piperidyl) - 1 - phenyl - 2 - indolinone hydrochloride* was obtained. M.pt. 279—281°

Analysis:

Calcd. for: $C_{26}H_{27}ClN_2O$:
C, 74.6; H, 6.51; N, 6.69%
Found: C, 74.42; H, 6.51; N, 6.52%

Example XIII

To a mixture of ethyl chloroformate (19.5 g; 17.2 mls; 0.12 mol.) and dry toluene (50 ml.) at 50°, was carefully added a solution of 3 - (1 - methyl - 4 - piperidyl) - 1 - phenyl - 2 - indolinone (18.3 g., 0.06 mole., prepared as in Example XI) in dry toluene (100 ml.). The mixture was heated under reflux for fifteen minutes. Thereafter the excess of ethyl chloroformate was boiled off until the temperature of the vapours reached 110°. The solution was then heated under reflux for three hours, followed by extraction with 2N HCl (2×50 ml.) in order to remove unchanged amino compound. The organic layer was evaporated *in vacuo* to give 9.4 g. of brown oil. This was mixed with 48% aqueous HBr (20 mls.) and acetic acid (60 mls.) and the resultant solution was heated under reflux for three hours. After evaporation of the solvents *in vacuo*, the resulting oil was dissolved in water, basified with 10% Na_2CO_3 solution and extracted with ether. The ethereal extracts were dried and treated with an ethereal solution of oxalic acid. A precipitate of crude oxalate (12.6 g.) was obtained, which was recrystallised from ethanol-methanol to yield 5.2 g. of pure *1 - phenyl - 3 - (4 - piperidyl) - 2 - indolinone hydrogen oxalate* as white crystals M.pt: 231—233°

Analysis:

Calcd. for: $C_{21}H_{22}N_2O_5$:
C, 65.95; H, 5.80; N, 7.33%
Found: C, 65.98; H, 5.81; N, 7.31%

The products of Examples VII and XIII inclusive have the ability to lower blood pressure in hypertensive animals.

Example XIV

3 - (3 - Methylamino - propyl) - 1 - indole hydrochloride (1.5g) was dissolved in water (5 ml.), basified with 5N NaOH and extracted into ether. The solvent was evaporated and the residual free base was taken into 10 ml. of dry tetrahydrofuran. This solution was added to liquid ammonia (80 ml.) and, while stirring under dry conditions, sodium (1 g.) was added in small pieces, each piece after the first being added as soon as the blue colour disappeared. The reaction was taken to be complete when the blue colour persisted for more than 7—10 minutes. Solid ammonium chloride was then added and the ammonia was evaporated slowly. The final solution was evaported *in vacuo* and the residual oil was taken up into dry ether. This solution was treated with ethereal oxalic acid solution and the precipitated oxalate was recrystallised once from isopropanol-water to yield 1.2 g. of *3 - (3 - methyl - amino - propyl) - 1 - phenyl - indoline hydrogen oxalate.*

M.pt: 179—180°

Calcd. for: $C_{20}H_{24}N_2O_4$:
C, 67.39; H, 6.79; N, 7.86
Found: C, 67.45; H, 6.75; N, 7.79

A small sample of the oxalate was converted into the free base and the mass spectrum was obtained showing a molecular ion of m/e 266, concordant with the calculated molecular weight.

The product of this Example has been found to have properties in common with anti-depressant drugs in experimental animals, to a more marked degree than those of the product of Example I.

The compound prepared in Example XIV has also been prepared according to the following Example:

Example XV

(1) Ethyl 3 - (3 - indolyl) propionate (21.7 g, 0.1 mol) was dissolved in glacial acetic acid (250 ml) and 2N HCl (50 ml., 0.1 mol) was added. This solution was hydrogenated at 60—70° and atmospheric pressure over a pre-reduced platinium oxide catalyst (20 g), stirring carefully throughout, until the theoretical amount of hydrogen had been ab-

sorbed. The catalyst was then filtered off and the solution evaporated under reduced pressure to a thick oil. This was washed with ether and the residual oil was carefully neutralised with Na_2CO_3 solution and extracted into ether. Evaporation of the dried ethereal extracts gave an oil which was distilled *in vacuo* at 150—155°/0.2 mm. mercury to yield 19 g. of *ethyl 3 - (3 - indolinyl) propionate.*

(2) Ethyl 3 - (3 - indolinyl -) propionate (15.33 g., 0.7 mol) was dissolved in tetrahydrofuran (50 ml.) and this solution was added carefully to a refluxing solution of lithium aluminium hydride (3.8 g., 0.1 mol) in tetrahydrofuran (200 ml.). The mixture was stirred and heated under reflux for 4 hours, and the complex was then destroyed by the addition of 3.8 g. of water, followed by 3.8ml. of 5N NaOH. The inorganic precipitate was filtered off and the solution evaporated to dryness when it yielded a thick oil. This was distilled *in vacuo* at 180—210°/0.2 mm mercury to yield 11.5g. of *3 - (3 - indolinyl) propanol.*

(3) To 3 - (3 - indolinyl) propanol (11.5g., 0.065 mol) dissolved in hexamethyl phosphoramide (100 ml.), cuprous bromide (0.1g.) and anhydrous K_2CO_3 (13.9g., 0.1 mol) were added. The mixture was heated to 170° and bromobenzen (15.7g., 0.1 mol) was added dropwise with stirring. The stirring and heating at 170—180° were maintained for 6 hours, when it was poured into a large volume of water and extracted with ether. The ethereal liquors were dried over K_2CO_3 and evaporated *in vacuo* to give a thick oil, which was distilled *in vacuo* at 210—220°/0.1 mm. mercury to yield 10g. of *1 - phenyl-3 - (3 - indolinyl) propanol.*

(4) 1 - Phenyl - 3 - (3 - indolinyl) propanol (10g., 0.044 mol) in dry benzene (50 ml.) was added to a cold mixture of pyridine (3.5g., 0.044 mol) and *p* - toluenesulphonyl chloride (8.4g., 0.044 mol) in benzene (50 ml.). The mixture was allowed to stand for 12 hours and then poured into water. The benzenic layer was dried over Na_2SO_4 and treated with a large excess of 33% ethanolic solution of methylamine (100 ml.) in a stainless steel bomb at 100° and left to stand for 12 hours.

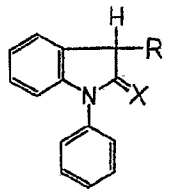
The mixture was then evaporated to dryness and the residue basified with 5N NaOH and extracted into ether. The ethereal solution was dried over Na_2CO_3 and evaporated to yield an oil. This was taken up into dry ether and treated with an ethereal solution of oxalic acid. The precipitate was recrystallised several times from isoproanol-water to give 8g. of pure *3 - (3 - methylamino - propyl) - 1 - phenyl - indoline hydrogen oxalate.* M.p. 179—180°.

Analysis:

Calculated for: $C_{20}H_{24}N_2O_4$— C, 67.39; H, 6.79; N, 7.86%
Found: C, 67.31; H, 6.99; N, 7.97%

WHAT WE CLAIM IS:—

1) A compound of the formula:



where (i) R represents *either* a group: $—C_nH_{2n}—NR^1R^2$, in which R^1 and R^2 each represent a hydrogen atom, a lower alkyl group or a benzyl group, or together with the nitrogen atom to which they are attached form a saturated heterocyclic ring containing at least 4 carbon atoms in the ring, which, if it contains a further nitrogen atom in the ring, may be substituted at such nitrogen atom with a lower alkyl or hydroxyalkyl group or a benzyl group, and C_nH_{2n} represents a lower alkylene group separating the nitrogen atom from the indoline ring by at least 2 carbon atoms; *or* a group: $—C_mH_{2m}—CHR^4$, in which m is from 0 to 4 and R^4 represents a bivalent group containing up to (7—m) carbon atoms and forming with the carbon atom to which it is attached a saturated heterocyclic ring containing at least 4 carbon atoms and at least one nitrogen atom, any such nitrogen atom being separated from the indoline ring by at least 2 carbon atoms and optionally carrying a lower alkyl or hydroxyalkyl group or a benzyl group;
(ii) X represents either an oxygen atom or two hydrogen atoms; and
(iii) any benzene ring (including the fused benzene ring) in the structural formula or in R^1, R^2 or R^4 may be substituted with one or more halogen atoms, lower alkyl or alkoxy groups, trifluoromethyl groups, nitro groups, hydroxyl groups or sulphamoyl or N - substituted sulphamoyl groups;
and the pharmaceutically acceptable acid addition salts of such compounds.

2) A compound as claimed in claim (1) in which R^1 and R^2 are each a hydrogen atom, a lower alkyl group or a benzyl group.

3) 3 - (3 - Dimethylaminopropyl) - 1 - phenyl - 2 - indoline and its oxalic acid addition salt.

4) 3 - (3 - Methylaminopropyl) - 1 - phenyl - indoline and its oxalic acid addition salt.

5) A compound as claimed in claim (1), in which R is a 3- or 4 - piperidyl group or a

2-, 3- or 4 - piperidyl - methyl group, or a 1 - lower alkyl or 1 - benzyl derivative of such a group.

6) A compound as claimed in claim (1), as prepared and characterised in Example I or in any of Examples VII to XIII.

7) A compound as claimed in claim (1), as prepared and characterised in Example XIV or Example XV.

8) A method of preparing a compound as claimed in claim (1), in which X is an oxygen atom and R represents the group $-C_nH_{2n}-NR^1R^2$ in which neither R^1 nor R^2 is hydrogen, which comprises reacting a compound of the formula II, as hereinbefore defined, with thallium metal or a thallous alkoxide in a suitable solvent and then with a compound of the formula hal—C_nH_{2n}—NR^1R^2, in which 'hal' represents a halogen atom.

9) A method of preparing a compound as claimed in claim (1), which comprises reacting a compound of the formula II, as hereinbefore defined, with an aldehyde or ketone having the formula IVA, IVB, or IVC, as hereinbefore defined, and reducing the unsaturated compound so formed to yield the required product.

10) A method of preparing a compound as claimed in claim (1), in which X is two hydrogen atoms and R represents the group $-C_nH_{2n}-NR^1R^2$, which comprises reacting a compound of the formula VIIA, as hereinbefore defined, with ammonia or an amine of the formula R^1R^2NH to form the corresponding amide and reducing the amide with lithium aluminium hydride to yield the required product.

11) A method of preparing a compound as claimed in claim (1), in which X is two hydrogen atoms and R represents the group $-C_nH_{2n}-NR^1R^2$, which comprises reacting a compound of the formula VIIB, as hereinbefore defined, in which the OH group is replaced by a 'leaving' group, ammonia or an amine of the formula R^1R^2NH.

12) A method of preparing a compound as claimed in claim (1), in which X is two hydrogen atoms and R represents the group $-C_nH_{2n}-NR^1R^2$, which comprises reducing a compound of the formula VIII, as hereinbefore defined, with sodium in liquid ammonia.

13) A compound as claimed in claim (1), when prepared by a method as claimed in any of claims (8) to (12).

14) A pharmaceutical composition comprising a compound as claimed in any of claims (1) to (7) or claim (13), and a pharmaceutical carrier therefor.

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